REMARKS

The Rejection of Claims 1, 6, 16-18, 26, 27, and 71-78 Under 35 U.S.C. § 112

Claims 1, 6, 7, 16-18, 26, 27, and 71-78 stand rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Applicants respectfully traverse.

Claims 1, 18, 72, and 73 are the independent claims of the rejected claim set. Claim 1 and 72 are directed to methods for making a hypermutable bacterium. A polynucleotide encoding a dominant negative mismatch repair (MMR) protein under the control of an inducible transcription regulatory sequence is introduced into a bacterium. The inducible transcription regulatory sequence in the bacterium is induced. The dominant negative MMR protein exerts a dominant negative effect on MMR when expressed in the bacterium. The bacterium becomes hypermutable. Claims 18 and 73 are directed to homogenous compositions of induced, cultured, hypermutable bacteria which comprise a polynucleotide encoding a dominant negative MMR protein under the control of an inducible transcription regulatory sequence. The dominant negative MMR protein exerts a dominant negative effect when expressed in the bacteria. Claims 1 and 18 recite that the dominant negative MMR protein is a truncated dominant negative PMS2 MMR protein. Claims 72 and 73 recite that the dominant negative MMR protein is a dominant negative PMSR or a dominant negative PMS2L MMR protein.

Compliance with the written description requirement of 35 U.S.C. § 112, first paragraph requires sufficient information in the original disclosure to convince an ordinarily skilled artisan that the inventor possessed the invention at the time of filing. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306 (Fed. Cir. 2003). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, (Fed. Cir. 1997). If the claimed invention recites a genus, the written description requirement for the claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the

applicant was in possession of the claimed genus. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997).

The final Office Action asserts that the claims are not adequately described because the specification and the art do not support the proposition that any protein from the PMS2, PMSR and PMS2L family of proteins (or truncated versions of PMS2), when expressed in any bacterium, interacts with the host bacterial mismatch repair mechanism so as to exert a dominant negative effect resulting in a hypermutability. Final Office Action at page 3, lines 9-12.

In fact, the specification satisfies the written description requirement by providing examples of the claimed methods of making a hypermutable bacterium and homogeneous compositions of induced, cultured, hypermutable bacteria using polynucleotides encoding a representative number of species of the genus of dominant negative MMR proteins in a representative number of bacterial species. Applicants also satisfy the written description requirement for the recited genus of polynucleotides encoding dominant negative MMR proteins through sufficient description of a representative number of species of the encoded proteins by identifying characteristics, *i.e.*, structure.

As discussed above, the specification discloses a representative number of species of dominant negative truncated PMS2 MMR proteins, dominant negative PMSR MMR proteins, and dominant negative PMS2L MMR proteins in a representative number of bacterial species. The specification discloses, in Example 2, that expression of human PMS2-134 or human PMSR3 in BL21 cells induces hypermutability. See page 26 at Table 1 and lines 14-17. Example 2 also discloses that DH5 alpha bacterial cells become hypermutable upon expression of *Arabidopsis thaliana* PMS2-134. See page 26, line 19 to page 27, line 4. Example 3 discloses that DH10B bacteria become hypermutable as a result of human PMS2-134 expression. See page 29, lines 4-7 and Table 2. Example 3 further describes that dominant negative mutants of PMSR2 and PMSR3 induce hypermutability in bacteria similar to human PMS2-134. Thus, the specification describes hypermutability as a phenotype resulting from expression of four species of the recited dominant negative MMR proteins, human PMS2-134, *A. thaliana* PMS2-134, PMSR2, and PMSR3, in three strains of bacteria, BL21, DH5 alpha, and DH10B.

Also as mentioned above, applicants satisfy the written description requirement for the claimed genus of dominant negative MMR proteins employed in the methods and compositions through sufficient description of a representative number of species by

identifying structural characteristics. The specification discloses that PMS2 truncation proteins, PMSR proteins and PMS2L proteins are highly homologous, *i.e.*, share a similar structure. The specification discloses that "the use of MMR genes, including the human PMSR2 and PMSR3 gene (ref 19), the related PMS134 truncated MMR gene (ref 32), the plant mismatch repair genes and those *genes that are homologous* to the 134 N-terminal amino acids of the PMS2 gene which include the MutL family of MMR proteins and including the PMSR and PMS2L homologs described by Hori et. al. (accession number NM_005394 and NM_005395) and Nicolaides (reference 19) [are useful] to create hypermutable microbes." Page 18, lines 8-16, emphasis added. Thus, the specification discloses that the species in the recited genus of dominant negative MMR proteins share a common structural feature, homology to the 134 N-terminal amino acids of the PMS2 protein.

Based on the description in the specification of identifying structural characteristics of a representative number of species of dominant negative MMR proteins expressed in hypermutable bacteria and based on specific exemplification of the claimed methods in which hypermutable bacteria are produced by expression of a representative number of species of dominant negative MMR proteins in a representative number of bacterial species, one of skill in the art would have understood that applicants possessed the claimed invention at the time of filing.

The Patent Office cites references Prudhomme, Kondo, and Nicolaides to support the rejection of the claims as not adequately described. The Office Action asserts that the claims are not adequately described because these references teach that one of skill in the art would not have been able to predict whether substitution of a disclosed species of the claimed dominant negative MMR proteins with another species that is not disclosed would yield a dominant negative mismatch repair protein in bacteria. Final Office Action at page 4, lines 7-12.

The Prudhomme reference is cited as teaching that expressing a *Streptococcus pneumoniae* homologue of the *Escherichia coli* MutL protein, HexB, in *E. coli* does not increase the mutation rate of the *E. coli*. Paper 20, page 4, line 21 to page 5, line 1. The Patent Office concludes that because the *S. pneumoniae* HexB protein does not increase mutation rates in *E. coli* cells, the function of the claimed genus of dominant negative MMR proteins also cannot be predicted based on their similar structure. Final Office Action at page 6, lines 16-19. The Office Action provides no reasoning to support its position that if full-

length structures of MutL homolog proteins cannot be substituted in bacteria to induce a dominant negative phenotype, then truncated PMS2 proteins, PMSR proteins, and PMS2L proteins cannot. As applicants have indicated, Claims 1 and 72 are directed to methods for making a hypermutable bacterium and compositions of induced, cultured, hypermutable bacteria that employ a polynucleotide comprising "a truncation mutation, wherein said dominant negative PMS2 mismatch repair protein is a truncated protein" (claim 1) or "a truncation mutation, and wherein said dominant negative mismatch repair protein is a truncated dominant negative PMS2 mismatch repair protein" (claim 72). Claims 18and 73 are similar to claims 1 and 72, but recite that the polynucleotide encodes a dominant negative mismatch repair protein "selected from the group consisting of a dominant negative PMSR and a dominant negative PMS2L mismatch repair protein." HexB, as taught by Prudhomme, is a full-length MutL homolog, similar to full-length PMS2, which is not the structure of the recited genus of proteins. The recited genus of mismatch repair proteins includes *truncated* PMS2 proteins, PMSR proteins, and PMS2L proteins. These proteins share structural homology that would be expected to affect a hypermutable phenotype in bacteria. See specification at page 18, lines 8-16, quoted above. Prudhomme does not teach a protein having a structure analogous to the recited structures, *i.e.*, a structure similar to a *truncated* PMS2 protein. Therefore, Prudhomme does not establish a reason to doubt that the claimed structures would predictably induce hypermutability.

The Patent Office cites the Kondo reference as teaching that PMS2L proteins are of unknown function and that knowledge of one PMS2L protein's function does not necessarily indicate another PMS2L protein's function. The Office Action asserts, "Kondo et al. stands for the assertion that PMS2Ls are unknown in function and even if through biochemical studies such function were resolved as to particular proteins within the hPMS2L family, such a result would not necessarily indicate how other members of the PMS2L family would function." Final Office Action at page 7, lines 16-19. Although Kondo teaches that the function of PMS2L proteins was unknown, Kondo also teaches structural characteristics of PMS2L proteins that would have lead one of skill in the art to predict that PMS2L proteins exert a dominant negative effect on a bacterial cell's mismatch repair function. Kondo teaches, "[PMS2L genes] are small genes with very high similarity to the 5' portion of *hPMS2*...The hPMS2-134 polypeptide contains the highly conserved amino-terminal domain of hPMS2 and structurally resembles PMS2Ls." Page 818, column 2, line 8 to page 819, column 1, line 6. See also figures 1B and 2, which provide a schematic of the structural

similarity of two PMS2L proteins to a PMS2 truncated protein and an alignment of the amino acid sequences of PMS2L proteins with PMS2, respectively. Kondo also teaches that the PMS2L proteins, like PMS2-134, do not bind MLH1. Kondo teaches, "Herein we report that hMLH1 does not interact with PMS2Ls but does interact with the carboxyl terminal portion of hPMS2." Page 819, column 2, lines 6-8. In fact, Kondo teaches that a PMS2-261 protein, which has a greater number of C-terminal amino acid residues than PMS2-134, does not interact with hMLH1. Kondo teaches that "this immunoprecipitation study clearly demonstrated that hMLH1 forms protein complexes in vivo with hPMS2 and hPMS2(203-862) but shows no interaction with hPMS2(1-261), PMS2L13(1-179), or PMS2L16(9-83)." Page 824, column 2, lines 41-45. Thus, Kondo teaches that PMS2L proteins are similar to human and *A. thaliana* PMS2-134, which are dominant negative for mismatch repair in bacteria. Based on Kondo's teachings, one of skill in the art would expect PMS2L proteins to also function as dominant negative mismatch repair proteins.

The Office Action asserts, however, that "Kondo et al. does not conclusively provide that PMS2Ls, expressed in mammalian cells (or bacteria), would necessarily lead to hypermutability." Final Office Action at page 4, lines 17-18. Applicants agree. Nonetheless, Kondo provides evidence in agreement with the teachings of the specification, that the PMS2L proteins are structurally similar to PMS2-134. Kondo further provides evidence that the PMS2L proteins are functionally similar to PMS2-134 because they do not bind MLH1. Thus, Kondo's teachings weigh in favor of applicants' assertion that PMS2L proteins exert a dominant negative effect on MMR in bacteria.

The Nicolaides reference is cited as teaching that "the function of PMSR genes is not definitively known" (final Office Action at page 5, lines 9-10) and that although applicants demonstrate that hPMSR3 induces hypermutability in bacterial cells, it "would not necessarily be predictive to other proteins having the prescribed functionality" (final Office Action at page 5, lines 11-12). Nicolaides, as noted above, teaches the identification of PMSR genes (PMS2 related genes). Nicolaides teaches that PMSR2, PMSR3, PMSR6, and PMS2L proteins are highly homologous to the N-terminal portion of PMS2, *i.e.*, the PMS2-134 deletion mutant. See Nicolaides Figure 5E. Thus, one of skill in the art would have predicted that the structurally similar PMSR proteins would also have a dominant negative effect on mismatch repair in bacteria.

Applicants respectfully submit that the Prudhomme, Kondo, and Nicolaides references provide no reason to doubt that substitution of any species of truncated PMS2

protein, PMSR protein, or PMS2L protein would function as a dominant negative mismatch repair protein in bacteria. Furthermore, applicants' exemplification of the claimed methods and compositions using representative species of the recited mismatch repair proteins in representative species of the recited bacteria (see, for example, Examples 2 and 3 of the specification) and disclosure of identifying structural characteristics of the recited dominant negative MMR proteins amply support the written description of the claims.

Applicants respectfully request withdrawal of the rejection.

The Provisional Doubling Patenting Rejection of Claims 16, 17, and 71

Claims 16, 17, and 71 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-3 and 36 of copending application serial number 09/912,697. Applicants respectfully request that the rejection be held in abeyance until the claims are indicated otherwise to be in condition for allowance.

Respectfully submitted,

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